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EXERCISING THE BRAIN IN PAIN

-USING FMRI TO INVESTIGATE INTRINSIC CONNECTIVITY, COGNITION AND PAIN REGULATION IN FIBROMYALGIA AND HOW THIS IS AFFECTED BY PHYSICAL EXERCISE

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Exercising the Brain in Pain

-Using fMRI to investigate intrinsic connectivity, cognition and pain regulation in fibromyalgia and how this is affected by physical exercise

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the participants who have courageously
participated in my studies.

ABSTRACT

The aims of the studies of this thesis were to use functional magnetic resonance imaging (fMRI) to investigate cerebral activation patterns in fibromyalgia (FM) patients and healthy controls (HC) at rest, when performing the stroop colour word test (SCWT) and during pressure pain provocation. Distraction induced analgesia (DIA), performance on the SCWT and pressure pain sensitivity was investigated on the behavioural and psychophysical level. Lastly studies III and IV investigated the effects of a 15-week resistance exercise training intervention on SCWT and pain processing.

The main finding in study I was that FM was associated with decreased connectivity between pain related and sensorimotor brain areas, more specifically between insula and primary sensorimotor areas (S1/M1). Furthermore increased pain sensitivity in both groups correlated to increased connectivity between the insula and thalamus with the default mode network (DMN).

Study II utilised the SCWT were participants are given colour words written in either congruent or incongruent colours. To induce DIA, participants were given two versions of the test, one with congruent words and one with incongruent words, this in order to investigate the impact of cognitive load on pain perception. In the scanner, the stimuli were mixed and presented in an event-related fMRI paradigm. The study revealed that DIA functioned the same in FM as it did in HC, and analgesia was not dependant on cognitive load. Performance on the SCWT showed that both groups were slower on the more cognitively demanding task, but interference disrupted performance more in the FM group than in the HC. The fMRI results yielded less activation of the caudate nucleus and hippocampus during SCWT in FM patients. These regions are implicated in learning and reward, suggesting that impaired learning mechanisms can contribute to the cognitive dysfunction often reported by FM patients.

In study III, the SCWT assessments were repeated following the physical exercise intervention. Performance on the SCWT was improved in both groups, in the HC speed of processing had improved significantly, but a specific improvement of cognitive ability was only found in the FM patients. The latter was accompanied by an increased activation of the amygdala following the intervention in the FM group. Regarding DIA, no effects of exercise were found.

Lastly, in study IV fMRI was used to assess pressure pain processing in FM patients and HC before and following the exercise intervention. FM patients were more pain sensitive than HC at both times, but following the intervention pressure pain sensitivity was significantly reduced in the FM group. We found no evidence that the exercise intervention had an effect on cerebral processing of evoked pain in either group. Our data suggest that the reduced pain sensitivity following exercise in FM patients was caused by peripheral mechanisms.

Taken together the results of the four studies all demonstrated aberrations in cerebral activation in FM patients compared to controls, as well as poorer cognitive performance and increased pain sensitivity. However, interestingly, normal function of DIA was found in FM patients. Studies three and four showed that physical exercise was beneficial to FM patients, both regarding cognitive ability and by reducing pain sensitivity.

LIST OF SCIENTIFIC PAPERS

I. Flodin P,. **Martinsen S**., Löfgren M., Bileviciute-Ljungar I., Kosek E., & Fransson P. (2014). Fibromyalgia Is Associated with Decreased Connectivity Between Pain- and Sensorimotor Brain Areas. Brain Connectivity*, 4 (8), 587-594*

II. **Martinsen S**., Flodin P,. Berrebi J., Löfgren M., Bileviciute-Ljungar I., Ingvar M., Fransson P., & Kosek E. (2014). Fibromyalgia Patients Had Normal Distraction Related Pain Inhibition but Cognitive Impairment Reflected in Caudate Nucleus and Hippocampus during the Stroop Color Word Test. PLoS One, *9 (10), doi:e108637*

III. **Martinsen S**., Flodin P,. Berrebi J., Löfgren M., Bileviciute-Ljungar I., Mannerkorpi, K., Ingvar M., Fransson P., & Kosek E. The role of long-term physical exercise on performance and cortical activation during the Stroop Color Word Task in Fibromyalgia patients. *In manuscript*

IV. **Martinsen S**., Flodin P,.Löfgren M., Bileviciute-Ljungar I., Mannerkorpi, K., Ingvar M., Fransson P., & Kosek E. Exercise reduces pain sensitivity but does not lead to altered pain related cerebral activation in fibromyalgia patients. *In manuscript*

CONTENTS

LIST OF ABBREVIATIONS

1RM	One Repetition Maximum
ACC	Anterior Cingulate Cortex
ACR	American College of Rheumatology
ANS	Autonomic Nervous System
BOLD	Blood-Oxygen-Level Dependent
CBT	Cognitive Behavioural Therapy
CLBP	Chronic Low Back Pain
CNS	Central Nervous System
CPM	Conditioned Pain Modulation
DIA	Distraction Induced Analgesia
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DNIC	Diffuse Noxious Inhibitory Controls
dACC	Dorsal Anterior Cingulate Cortex
EAN	Executive Attention Network
EEG	Electroencephalography
EIH	Exercise Induced Hypoalgesia
fALFF	Fractional Amplitude of Low Frequency Fluctuation
FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
HADS	Hospital Anxiety and Depression Scale
HADS A	Hospital Anxiety and Depression Scale Anxiety
HADS D	Hospital Anxiety and Depression Scale Depression
HC	Healthy Control
IASP	International Association for the Study of Pain
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
IPL	Inferior Parietal Lobe

ISI	Inter-Stimulus Interval
MI	Primary Motor Cortex
MNI	Montreal Neurological Institute
n.a.	Not applicable
NS	Nociceptive Specific
n.s.	Non-Significant
OA	Osteoarthritis
OBFC	Orbitofrontal Cortex
PAG	Periaqueductal Grey
PASAT	Paced Auditory Serial Attention Test
PCC	Posterior Cingulate Cortex
PGIC	Patient Global Impression of Change
PPT	Pressure Pain Threshold
PT	Physiotherapist
rACC	Rostral Anterior Cingulate Cortex
rCBF	Regional Cerebral Blood Flow
rEAN	Right Executive Attention Network
ROI	Region of Interest
RT	Reaction Time
SI	Primary Somatosensory Cortex
SII	Secondary Somatosensory Cortex
SCA	Seed Correlation Analysis
SCWT	Stroop Colour Word Test
SF 36	Short Form 36
SF 36 PCS	Short Form 36 Physical Compact Score
SF 36 MCS	Short Form 36 Mental Compact Score
SMA	Supplementary Motor Area
SNRI	Serotonin-Noradrenaline Re-uptake Inhibitor
SPECT	Single Photon Emission Computed Tomography
TEA	Test of Everyday Attention
VAS	Visual Analogue Scale

VLPFC	Ventrolateral Prefrontal Cortex
WDR	Wide Dynamic Range
WM	Working Memory

1 INTRODUCTION

Acute nociceptive pain can be seen as a warning sign of injury or illness and there is often a relationship between the degree of injury and the pain intensity, but in chronic pain the relationship between peripheral pathology and the severity of pain symptoms is less clear. It has been proposed that chronic musculoskeletal pain can persist even with a minimal amount of peripheral pathology as a result of abnormalities in central pain modulation, such as in fibromyalgia (FM) (Clauw, 2014). Recently, a number of neuroimaging studies have been performed in FM patients and these have revealed aberrations in pain modulation, altered resting state patterns as well as structural changes such as reductions in cortical thickness and grey matter volume (Jensen et al., 2009, Napadow et al., 2010, Cifre et al., 2012, Jensen et al., 2013, Pujol et al., 2014). These results have led to a general acceptance that there are central nervous system (CNS) disturbances affecting pain modulation in FM. In accordance with this, many of the currently recommended treatments for FM, i.e., cognitive behaviour therapy and pharmacotherapy with serotonin-noradrenalin re-uptake inhibitors or anticonvulsants target the CNS mechanisms (Carville et al., 2008). In addition, cognitive difficulties have been observed in FM, frequently referred to as "fibrofog", and there is considerable overlap between areas in the brain concerned with pain regulation and cognition (Glass et al., 2011). As opposed to the extensive research on pain processing in FM, the cognitive aspects of FM have received less attention and to date only few studies of cognitive processing investigated with neuroimaging have been published. In addition to the evidence of CNS abnormalities in FM, there are also reports of muscle pathology including aberrations in muscle metabolism (Kalyan-Raman et al., 1984, Bengtsson et al., 1986, Elvin et al., 2006, Gerdle et al., 2014) and peripheral nerve fibre pathology (Uceyler and Sommer, 2013, Serra et al., 2014) suggesting a complex interaction between peripheral and central mechanisms in the pathophysiology of the FM syndrome. The latter is in line with physical exercise as a cornerstone in FM treatment (Carville et al., 2008). It has been acknowledged that exercise

has a positive impact on both physical and mental health in the general population, and it also has an analgesic effect, both acutely and long-term (Koltyn and Umeda, 2006, Hillman et al., 2008, Hassett and Williams, 2011). The aim of this thesis was to use functional magnetic resonance imaging (fMRI) to investigate differences in resting state activity, cognitive performance and central pain modulation between FM patients and healthy controls and to study the central effects of long-term physical exercise.

1.1 FIBROMYALGIA (FM)

1.1.1 Classification of FM

FM patients were included in all studies of this thesis. Currently, there are two sets of classification criteria proposed by the American College of Rheumatology (ACR), the 1990 and the 2010 criteria (Wolfe et al., 1990, Wolfe et al., 2010). The 1990 criteria were intended for research purposes, whereas the 2010 criteria came about as an effort to make the criteria more useful in a clinical environment. The acceptance and international use of the ACR 1990 criteria has had a great importance in research, since using uniform criteria reduces the heterogeneity of the patient cohorts. In this thesis the ACR 1990 criteria (Box 1.1) was consequently adhered to. The ACR 2010 criteria differ from the ACR 1990 by eliminating the tender point count, the only item requiring physical examination. Instead these criteria rely on a count of the number of body regions reported as painful by the patient, and ratings of the severity of a number of symptoms regarded as important in FM, i.e., fatigue, non-refreshed sleep, cognitive problems, and the extent of somatic symptom reporting. The ACR 2010 criteria are controversial and have not yet been internationally accepted for research purposes.

1.1.2 The clinical presentation of fibromyalgia

Using the ACR 1990 criteria for classification of FM, the prevalence of FM in the general population is approximately 2 % (Wolfe et al., 1990) with a female dominance (80%) (Yunus

Box 1.1. The 1990 American College of Rheumatology criteria for the classification fibromyalgia (Wolfe et al. 1990).

1. History of widespread pain

Definition: Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. 'Low back' pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation

Definition: Pain, on digital palpation, must be present in at least 11 of the following 18 sites:

Occiput: Bilateral, at the suboccipital muscle insertions.

Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5 – C7.

Trapezius: bilateral, at the mid-point of the upper border.

Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.

Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.

Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.

Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.

Greater trochanter: bilateral, posterior to the trochanteric prominence.

Knee: bilateral, at the medial fat pad proximal to the joint line.

Digital palpation should be performed with an approximate force of 4 kg.

For a tender point to be considered 'positive' the subject must state that the palpation was painful. 'Tender' is not to be considered 'painful'.

For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

2001). FM patients suffer from chronic, migrating, widespread pain, mainly localized to muscles although joint pain can be present (Wolfe et al., 1995). Typically, the pain is augmented by physical exercise or stress (Kadetoff and Kosek, 2007). In addition to widespread pain, fatigue, disturbed sleep and cognitive problems (Bennett, 2009, Glass, 2009) are major symptoms in FM. The sleep disturbance in FM is characterized by non-refreshing sleep, frequent nightly awakenings and reduced levels of non-REM deep sleep

when assessed by electroencephalography (EEG) (Horne and Shackell, 1991). Typical cognitive dysfunctions in FM are difficulties to concentrate, memory disturbances, stress intolerance and reduced simultaneous capacity (White et al., 1999).

1.2 PAIN PERCEPTION

In order to understand pain processing it is important to understand the terms "pain" and "nociception", and how these are separable. Nociception is described in the taxonomy of the international association for the study of pain (IASP) as the following (see IASP webpage):

"The neural process of encoding noxious stimuli."

and also that

"…pain sensation is not necessarily implied."

It might seem counter-intuitive that a potentially dangerous stimulation is not always experienced as painful, however noxious stimuli can activate nociceptors without reaching consciousness.

The IASP taxonomy describes pain as:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

And it continues to say

" Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain."

Finally, IASP defines pain thresholds as:

"The minimum intensity of a stimulus that is perceived as painful."

And it goes on to elaborate:

” Properly defined, the threshold is really the experience of the patient, whereas the intensity measured is an external event.”

The IASP taxonomy establishes that pain is a subjective experience that cannot be objectified purely in terms of nociception and it also establishes that the pain threshold is a measure based on the participant’s experience. Pain is moulded through past experiences and this will influence the response to even the most rigorously controlled experimental situation. It is not unlikely that a patient will come into the experimental setting with a different set of expectations than a healthy control, based upon living with their disorder, however, these expectations are a part of the multi-modal experience of pain and should be taken into account when performing sensory testing.

1.3 CENTRAL PAIN PROCESSING AND DESCENDING PAIN INHIBITION

There are two types of fibers that carry nociception from the periphery, Aδ-fibers and C-fibers. Aδ-fibers are myelinated enabling the nociceptive signal to travel fast. The signal carried by Aδ-fibers is often experienced as sharp and localised pain. C-fibers are unmyelinated, meaning that the nociceptive signals take longer to reach the CNS and therby awareness. C-fiber activation typically results in a more blunt, throbbing pain (Dostrovsky and Craig, 2005, Kosek, 2014). The primary afferent nociceptors, Aδ- and C-fibers, reach the dorsal horn of the spinal cord where they synapse with secondary afferent neurons, nociceptive specific (NS) neurons and wide-dynamic range (WDR) neurons. To simplify, it can be said that following the first synapse, the nociceptive signals travel mostly along paths reaching the thalamus. The majority of the axons travel along tractus spinothalamicus, to the lateral parts of the thalamus where they synapse with neurons projecting to the sensory cortices. Other axons travel along tractus spinoreticularis, synapse at the reticular formation with neurons projecting to the medial parts of the thalamus, in turn forming synaptic connections with neurons projecting to structures such as the anterior cingulate cortex (ACC),

insula and prefrontal cortices (Dostrovsky and Craig, 2005, Kosek, 2014). These two systems are often referred to as the lateral- and medial pain network. The lateral network is primarily concerned with the sensory processing of pain, whereas the medial network is mainly implicated in the cognitive-emotional-evaluative aspects of pain processing (Dostrovsky and Craig, 2005, Kosek, 2014).

The perception of pain is highly complex and important for regulating these experiences are descending pain inhibitory circuits, where the periaqueductal grey (PAG) is key. PAG receives both ascending nociceptive input from the spinal tract via the medulla as well as receiving top-down modulatory signals from the insula, amygdala, thalamus, cingulate cortex and more frontal regions. PAG projects via the rostroventral medulla to the dorsal horn of the spinal cord where the signal interacts with and regulates nociceptive input from the periphery (Tracey and Mantyh, 2007).

1.3.1 Pain regulation in FM

One of the major characteristics of FM patients is that they are more sensitive to painful stimuli than healthy subjects. Increased pain sensitivity in FM patients has been reported for cutaneous (heat/cold) as well as deep (pressure) stimuli at threshold as well as suprathreshold intensities. (Kosek et al., 1996c) Furthermore, dysfunctions of endogenous pain inhibitory mechanisms have been reported in FM patients (Kosek and Hansson, 1997, Lautenbacher and Rollman, 1997, Lannersten and Kosek, 2010). One frequently used method to investigate endogenous pain inhibition is to study the sensitivity to a noxious test stimulus before and during a noxious conditioning stimulus in a heterotopic part of the body, i.e., “pain inhibits pain”, or conditioned pain modulation (CPM), previously referred to as diffuse noxious inhibitory controls (DNIC).

Typically, the cold pressor- or the tourniquet tests have been used as conditioning stimuli and pressure pain thresholds (PPTs) as the test stimuli in previous studies. The increase in PPTs

during the conditioning stimulus, compared to baseline is taken as a measure of CPM. In previous studies, increases in PPTs signifying CPM have been reported in healthy controls and in patients suffering from rheumatoid arthritis (RA) (Leffler et al., 2002), but not in patients suffering from FM (Kosek and Hansson, 1997, Lautenbacher and Rollman, 1997), indicating a dysfunction of endogenous descending pain inhibitory mechanisms in FM. However, the fact that dysfunctional CPM has also been reported in patients suffering from painful osteoarthritis (OA) but normalized following successful treatment (surgery) indicates that this dysfunction is not specific for FM, that it can be caused or maintained by a nociceptive input and that it is reversible (Kosek and Ordeberg, 2000, Arendt-Nielsen et al., 2010, Graven-Nielsen et al., 2012).

Another frequently used method to study endogenous pain modulation is to use isometric muscle contractions as conditioning stimuli and assess the effects on noxious test stimuli at the contracting muscle or at a distant resting muscle, i.e., exercise induced hypoalgesia (EIH) (Koltyn, 2002). A dysfunction of EIH has been found in FM patients (Kosek et al., 1996a, Staud et al., 2005, Lannersten and Kosek, 2010) as well as patients suffering from localized myalgia during contractions of the affected muscles, but not during contraction of healthy muscles (Lannersten and Kosek, 2010). Normal EIH has been reported in RA patients (Friden et al., 2013) as well as OA patients (Kosek et al., 2013), indicating that this dysfunction may be related to muscle-, but not joint pain states. Given that the isometric contractions can be painful, it has been speculated if EIH is one form of CPM. Contradicting this is that EIH is induced even when the contraction is not experienced as painful (Ellingson et al., 2014) suggesting that the mechanisms behind CPM and EIH are separate.

1.4 COGNITION AND FM

1.4.1 "Fibrofog"

Cognitive problems and pain are frequently co-occurring (for a comprehensive review see Moriarty et al., 2011), and the cognitive impairment in FM is frequently referred to as

"fibrofog". The word fibrofog is a lose term, but Leavitt and colleagues defined it as "the combination of complaints of memory problems and mental confusion" (Leavitt et al., 2002). Leavitt et al. investigated self-reported memory decline, mental confusion and a combination of both, as well as dissociation symptoms in patients with rheumatic disease comorbid with FM and rheumatic disease patients without FM. They could report that the occurrence of one or both complaints of memory decline and mental confusion was significantly higher in FM patients compared to the controls. In addition no differences in age, education or depression were found between FM patients with and without cognitive complaints, indicating that these factors could be ruled out as explanatory variables. FM patients also scored higher on dissociation (alterations of sensory experiences), which disrupts cognition both in terms of perception as well as memory. The authors found that high scores on dissociation correlated with more severe clinical symptoms (pain and fatigue) as well as with a higher degree of mood disturbances (tension, depression and anger). Notably, the FM patients had significantly higher pain scores than non-FM controls (Leavitt et al., 2002). The same group elaborated on this study in 2004, investigating memory decline, mental confusion and speech difficulty, and could again report higher prevalence of one or a combination of these complaints in FM patients compared to non-FM controls and 51% of the FM patients met the authors criteria for fibrofog (mental confusion and memory decline in combination) in comparison to 8% of the controls. Furthermore, FM patients meeting the criteria for fibrofog had higher intensity of pain than those reporting only memory related problems or no cognitive symptoms (Katz et al., 2004). These data support the relationship between reported pain intensity and fibrofog.

1.4.2 Cognitive performance in FM syndrome

Previous studies regarding specific aspects of memory and cognitive performance indicate that FM patients are mostly impaired on tasks tapping onto working memory (WM) and distraction (Glass, 2009). This is in line with Leavitt and colleagues' suggestion from 2002

that tests only investigating memory do not suffice to detect "fibrofog" or cognitive impairment in FM patients, as there are not sufficient distractions in these tasks (Leavitt et al., 2002), and in 2006, Leavitt and Katz published a study showing that memory impairment in FM patients was larger when there was a distractor involved (Leavitt and Katz, 2006). The test of everyday attention (TEA) assessing attention and WM has been found to have a good face validity (Dick et al. 2002). The TEA was implemented in four different cohorts, FM patients, RA patients, and a group of patients suffering from other musculoskeletal disorders (not FM or RA) as well as healthy controls. No difference was found on overall TEA score between the pain groups, however they all performed worse than the healthy controls (Dick et al., 2002). As opposed to the previously reviewed studies (Leavitt et al., 2002, Katz et al., 2004) no difference in pain scores was found between the patient groups, which could explain the similarities in cognitive performance. Compared to healthy controls (HC) the FM patients performed worse on all subscales of the test (selective attention, sustained attention and WM) bar attention switching. The same group published a study in 2008 reporting that interference interrupted performance increasingly as the tasks became more demanding, which was independent of mood or sleep, but when controlling for pain, the effects were abolished, again pointing towards that pain is contributing factor to fibrofog (Dick et al., 2008). They could also report that fibrofog is not likely a global cognitive decline, but specific to WM and further that WM capacity could predict overall attentional function (Dick et al. 2008).

1.5 NEUROIMAGING STUDIES OF FM

Neuroimaging studies have significantly contributed to our understanding of the central mechanisms of FM. First it became evident that it was perceived pain that correlated to cerebral activation patterns and not the absolute stimulus intensity (Gracely et al., 2002). Also alterations in cerebral activation patterns in response to evoked pain thought to be related to dysfunctional pain modulation in FM have been reported (Gracely et al., 2002, Jensen et al.,

2009). Neuroimaging studies have also played an important role in understanding the cerebral mechanisms behind interventions frequently used to treat FM, such as the serotonin-noradrenaline re-uptake inhibitor (SNRI) milnacipran (Jensen et al., 2014) and cognitive behavioural therapy (CBT) (Jensen et al., 2012a).

1.5.1 Resting state studies of FM

Mountz et al (1995) performed a study using single photon emission computed tomography (SPECT) comparing cerebral blood flow at rest in women with FM with HC. They could report less blood flow in the caudate nucleus and thalamus in FM, and were first to relate increased pressure pain sensitivity to altered cerebral activation (Mountz et al., 1995). Following Mountz and colleagues SPECT study on the resting brain, several resting state studies in FM have followed. For instance Kwiatek (Kwiatek et al., 2000) found reduced regional cerebral blood flow (rCBF) in the thalamus, but not the caudate, and Gur et al. could report higher rCBF of the caudate in FM, hence the findings regarding the caudate are not uniform (Gur et al., 2002). In later years, fMRI resting state studies have been performed, for instance Napadow and colleagues (2010) looked at the resting brain in FM patients comparing it with HC and found that FM patients showed higher connectivity between the default mode network (DMN) and right executive attention network (rEAN) to the insular cortex (Napadow et al., 2010). The insular cortex is known to activate during provoked pain and has been proposed to work as an internal thermostat for introspection (Craig, 2009). The increased connectivity could lead to a different response of the DMN to sensory input thus altering processing of sensory information (Napadow et al., 2010). In support of this, Napadow and colleagues reported that improvement of FM symptoms was accompanied by reduced connectivity between the DMN and the insula (Napadow et al., 2012). Cifre et al. in 2012 performed a study looking at connectivity between specific regions often associated with pain. They could identify a number of alterations in the brain's connectivity at rest in FM patients compared to controls, both increases and decreases of functional connectivity

between seed regions implicated in pain and the rest of the brain. Also this study could report increased insular connectivity in FM patients, but with the ACC and PAG. Increased resting state connectivity in the patients was also found between primary motor areas to the supplementary motor areas and the ACC to the caudate nucleus. Finally, they reported decreased connectivity between the insula to thalamus, the ACC to the amygdala and the posterior cingulate cortex (PCC) to the superior temporal sulcus (Cifre et al., 2012). Mixed findings of increased and decreased connectivity in FM were also reported by Pujol and colleagues, who specifically investigated the PAG due to its critical role in descending pain inhibition, parietal operculum/secondary sensory cortex (SII) and their connectivity with the DMN. Decreased connectivity in FM was found between PAG to the anterior insula as well as the parietal operculum to the primary somatosensory (SI), visual and auditory cortices. Increased connectivity was found between the SII and DMN. Furthermore, certain measures of connectivity were correlated with clinical pain, and the authors suggested that this indicated generally worse sensory integration in FM (Pujol et al., 2014).

1.5.2 Investigating pain processing in FM

In 2002 an fMRI study was published that directly related the increased pressure pain sensitivity to augmented cerebral processing in FM (Gracely et al., 2002). During low intensity pressure stimuli, 12 brain areas were activated in the patients, whereas in the healthy controls only two regions became activated. Importantly there was a difference of perception between the groups, i.e. the stimulus was experienced as painful in the FM patients, whereas this was not the case in the HC. The healthy controls also underwent scanning with a painful pressure eliciting similar pain intensity as the FM patients experienced, and when comparing the painful condition in both groups, the authors reported attenuated response in the caudate nucleus and thalamus in FM patients compared to controls. A second study was published in 2009 by Jensen and colleagues using an event-related fMRI paradigm, where both FM patients and controls were presented with both non-painful and individually calibrated

pressure pain stimuli. They reported decreased thalamic activity in FM patients, but also decreased activity of the rostral ACC (rACC). Furthermore they could correlate the response of the brainstem, which is highly implicated in descending pain inhibition, to rACC activity (Jensen et al., 2009). The rACC is an area involved in descending pain inhibition, as is the thalamus, and less activity in this region was interpreted as a sign of dysfunctional endogenous pain inhibition in FM (Jensen et al. 2009). Cortical thickness as well as grey matter volume has also been reported to be reduced in the rACC, overlapping with the area showing attenuated activity in the patients (Jensen et al., 2013). Interestingly, in addition to the overlap between the structural and functional brain changes in FM patients, the reductions of brain volume have been reported to increase with increased duration of the FM duration (Jensen et al. 2013). Functional connectivity has also been studied in FM where the rACC was found to show less functional connectivity to the amygdala, hippocampus and the brain stem, and the thalamus to the orbitofrontal cortex (OBFC) (Jensen et al., 2012d). Recently a study on the anticipatory processing of pain and pain-relief was published where participants were cued for both onset of pain as well as pain relief prior to and following induced pain using a cuff on the leg (Loggia et al., 2014). The duration of painful stimulation was 46-76 seconds, considerably longer than the 2.5 seconds used by Jensen and colleagues (Jensen et al., 2009). The authors did not report any differences between FM patients and HC during pain provocation, which can be a reflection of the differences in study design. The authors reported differences between the groups when anticipating both pain and its relief, specifically less activation in the FM patients compared to controls. Most notable was the ventral tegmental region, which was significantly more activated in the controls when anticipating pain, and deactivated when anticipating pain relief and this was not evident in FM patients. This is also a region that is rich in dopamine, suggesting a role of altered dopaminergic neurotransmission in FM patients. Other regions showing less activity in the patients when anticipating pain, included the cingulate cortex, PAG and also here the caudate

(Loggia et al., 2014). Less activity of the ACC and PAG is in line with findings of alterations in descending pain inhibitory circuits, as these are regions highly implicated in descending pain inhibition (Tracey and Mantyh, 2007). This could suggest a failure in activating descending pain modulatory systems in FM when expecting painful stimulation.

1.5.3 Investigating cognitive processing in FM

To the author's knowledge, three studies have been conducted investigating cerebral activation patterns in FM when performing a cognitive task. Glass and colleagues were first in 2011 where they used a Go/No-Go task, which is a response-inhibition task tapping on executive functioning. The authors state that this task was chosen in order to investigate areas that have shared functioning between cognition and pain processing, such as the supplementary motor area (SMA) and the ACC (Glass et al., 2011). On the behavioural level no difference was found regarding wrong responses or reaction times (RTs) between the groups. Structures involved in response selection (SMA, premotor cortex) and attention (inferior parietal lobe (IPL), premotor cortex, insula and inferior frontal gyrus (IFG)) were found to be hypoactivated in the patients compared to controls. Hyperactivity was found in the inferior temporal cortex/fusiform gyrus in FM patients compared to controls. Considering this and that behavioural data did not differ between the groups the authors proposed some compensatory brain plasticity in the patients in order to perform on par with the controls. Seo and colleagues published an fMRI study where they had given FM patients and controls a WM task (n-back) (Seo et al., 2012). In this study FM patients showed poorer performance compared to controls both in regard to accuracy and RTs. Further, they did a small volume correction in regions of interest (ROI) between the groups and found that the ventrolateral prefrontal cortex (VLPFC), superior frontal cortex, thalamus, ACC and IPL showed less activity in the FM group compared to controls. In the main effects analysis (0-back compared to 2-back) in the two groups separately, the authors reported higher activity of the caudate nucleus in the controls, however this region was not included in their ROI analysis, so

whether this difference is statistically significant cannot be inferred from the study (Seo et al., 2012).

The last study that will be brought up concerning fMRI, cognition and FM is a follow-up study to Glass et al. (2011) where it was reported that improved pain scores correlated with increased activity of the ACC and SMA during the Go/No-Go task in FM patients, i.e., a sign of normalization (Schmidt-Wilcke et al., 2014). This study was performed on the same cohort as the study from 2011, however the participants had participated in a number of different interventions so the mechanisms behind this improvement is unknown.

1.5.4 Investigating treatment effects in FM

Neuroimaging studies have even contributed to our understanding of the different effects of interventions on FM. Jensen et al performed a study where patients where either randomized to CBT or a waiting list. They underwent fMRI scanning with both painful and non-painful pressures on the thumb before and following the intervention, or 12 weeks on the waiting list. CBT did not alter pressure pain sensitivity, but clinical improvement (as measured by the patient global impression of change (PGIC)) was detected as was reduced anxiety in the group receiving CBT. The authors could also show increased pain related activity of the VLPFC)/lateral OBFC, which are areas of the brain that are associated with executive cognitive control. Furthermore, increased connectivity was found between this same region to the thalamus following the intervention. This increase in activity was interpreted as a possible improvement in FM pathophysiology, considering earlier findings of attenuated thalamic activity (Jensen et al., 2012b). But not all interventions are the same, the same group did a placebo controlled intervention study using milnacipran, an SNRI, and in this study it was possible to segregate the responders to milnacipran from placebo responders, as well milnacipran non-responders, again measured by PGIC. Regarding pressure pain sensitivity, only milnacipran responders had decreased sensitivity following the intervention, whereas no change was detected in either milnacipran non-responders or placebo responders. In the brain,

increased pain related activity was found in the PCC in milnacipran responders and this was related to the degree of clinical improvement. No change in PCC activation was found in either of the other groups (Jensen et al., 2014). Lastly a placebo-controlled study on the anti-convulsant pregabalin, where PET, resting state fMRI and pain evoked fMRI data were collected, reported that treatment with pregabalin reduced glutamate and glutamine in the posterior insula. Furthermore reduction of clinical pain following pregabalin treatment correlated with reduced activity between this region and the IPL and PCC, areas within the DMN (Harris et al., 2013). This is in line with the previously mentioned resting state study by Napadow and colleagues who reported reduced connectivity between the insula and DMN correlated with reduced clinical pain (Napadow et al., 2012). Furthermore the PCC and IPL displayed greater deactivation during evoked pain following pregabalin, but not placebo (Harris et al., 2013).

1.5.5 Cross-sectional studies on physical activity in FM

Physical activity is recommended in FM, and two cross-sectional studies have been performed investigating brain responses correlating to physical activity in FM. Physical activity was measured using self-report and accelerometer activity. A negative correlation was found between physical activity and pain ratings, and there was a positive relationship between physical activity and pain evoked activity in the dorsolateral prefrontal cortex (DLPFC), PCC and posterior insula, as well as a negative relationship between the primary sensory and superior parietal cortices (McLoughlin et al., 2011). An elaboration on this study was made later using SCWT to study DIA in FM patients in relation to physical activity. The authors found that physical activity was associated with a better function of DIA and activation of several brain regions, including the DLPFC (Ellingson et al. 2012). However it should be kept in mind that these studies are cross-sectional and the direction of the relationship between physical activity and pain modulation cannot be inferred. I.e. whether physical activity leads to a better ability to modulate pain or if enhanced pain modulation

allows for a higher degree of physical activity.

1.6 EXERCISE

Pain processing and cognition are both affected by physical exercise, acutely and long- term. Exercise has both broad and specific effects on cognition meaning that physically fit individuals perform better overall on measures of cognitive functioning, but it specifically has a larger impact on executive functioning (see Hillman et al., 2008 for a very comprehensive review on the subject). As mentioned above, hypoalgesia is induced following exercise in healthy individuals (Koltyn and Umeda, 2006), and physical exercise is considered an effective treatment for chronic pain (Hassett and Williams, 2011). Most research has been done on aerobic exercise, but there is evidence for resistance training having beneficial effects on both clinical outcomes as well as mood in FM (Gavi et al., 2014).

1.6.1 Exercise and FM

Physical exercise is a corner-stone in treating FM syndrome, a meta-analysis reported that aerobic exercise has a positive impact on global well-being, physical function and pain (Busch et al., 2007). FM patients engage in less strenuous activities than sedentary controls (Kop et al., 2005), and cardiovascular fitness has been reported to be below average in FM (Burckhardt et al., 1989). The effect of exercise on cognition in FM is of particular interest, as executive functioning appears to be the measure that exercise has the greatest effect on (Hillman et al., 2008). The cognitive symptoms reported in FM, which seemingly appear to be related to WM and executive functioning, should therefore be particularly susceptible to improvement in FM following exercise. In line with this, improved cognitive functioning has been reported following aquatic exercise alongside improved pain related symptoms in FM (Munguia-Izquierdo and Legaz-Arrese, 2007, 2008). More specifically, they reported improvement on the paced auditory serial attention test (PASAT), which is a test on both attention as well as WM, which are closely linked to executive functioning (Glass, 2009).

2 AIMS AND HYPOTHESES

The thesis has two general aims. Firstly to investigate brain activation patterns in FM patients and HC during rest, the SCWT and pressure pain provocation using fMRI. Secondly to investigate the effects of a 15-week physical exercise program on performance on the SCWT, pain sensitivity as well brain activation during pressure provocation.

2.1 STUDY I

The aims of this study were to reproduce and to expand on the studies that previously have been done on resting state connectivity in FM syndrome. More specifically aiming to reproduce Napadow et al's (2010) findings of increased connectivity between the insula and DMN as well as the insula and executive attention network (EAN) in FM patients. Furthermore a seed correlation analysis (SCA) was performed as well as a fractional amplitude of low frequency fluctuations (fALFF) analysis in order to investigate if the findings of (Kim et al., 2013) could be reproduced. Lastly the relationship between pressure pain sensitivity and resting state connectivity was investigated.

2.2 STUDY II

There were two aims of this study, first to use SCWT to investigate distraction induced analgesia (DIA) in FM and HC, and second, to assess performance and cerebral activation patterns related to the SCWT using fMRI. Earlier studies have found increased DIA during a higher cognitive load, which was partially related to ACC activation (Floden et al., 2010). Therefore we hypothesised that if FM patients have a normal ability to activate the ACC during cognitive tasks, the increase of cognitive load during the incongruent condition would lead to increased DIA in both patients and controls. Alternatively it was hypothesised that FM patients might have a generally reduced ability for ACC activation during a cognitive task in which case no DIA would be expected in the patient group.

In the second part of the study, participants did the SCWT during fMRI. Slower RTs were expected for incongruent than for congruent stimuli in both groups, as well as poorer cognitive performance in the FM group. In healthy individuals, poor performacence on the SCWT was related to higher task related ACC and lower DLPFC activation (Floden et al., 2010). Based on these findings, we hypothesized that if the dysfunction of the ACC in FM patients was not general, the poor performance would be reflected cerebrally as less activity of the DLPFC and more activity in the ACC in FM patients compared to controls. However if FM patients have a general ACC dysfunction, the reciprocity between ACC and DLPFC would not be found.

2.3 STUDY III

This study aimed to address the effects of a 15-week physical resistance exercise program on DIA in FM and HC, as well as performance and cerebral activation patterns related to the SCWT. The results from study II yielded no differences between patients and controls in regard to DIA; hence we did not expect to find any differences following exercise in this regard.

Based on previous reports of beneficial effects of physical exercise on cognitive function in healthy controls (Hillman et al., 2008) and our findings of slower cognitive processing in FM patients related to task difficulty, we hypothesised that RTs during SCWT would improve in both groups following the exercise intervention but that this would be particularly pronounced during the incongruent stimuli in FM patients. Furthermore, given our findings in study II of reduced activation of the caudate nucleus and hippocampus in FM patients during SCWT, we hypothesized that the cognitive improvement would be reflected as an increased or normalised activation of the caudate nucleus and hippocampus. Based on the same reasoning as in study II, improved performance on the SCWT was also hypothesised to be reflected as an increased activity of the dlPFC and decreased activity of the ACC in the HC.

2.4 STUDY IV

The main aim of study IV was to use fMRI to investigate the impact of a 15-week physical resistance exercise program on pain sensitivity and cerebral pain processing in FM. We expected FM patients to have an increased sensitivity to pressure pain compared to healthy controls. Baseline fMRI assessments during individually calibrated pressure pain of moderate intensity were hypothesised to yield less activity of the thalamus and rACC as has been found previously in FM patients (Jensen et al. 2009), indicating a reduced activation of descending pain inhibitory mechanisms. Exercise was hypothesised to improve FM symptoms, clinical pain and reduce pain sensitivity (Busch et al., 2007). If these improvements were mediated by peripheral or spinal mechanisms, we hypothesized that higher absolute pressures would be needed to elicit the moderate pain, but that no changes in cerebral pain related activation would be seen. On the other hand, exercise related changes in cerebral pain processing would be identified by our fMRI method.

3 MATERIALS AND METHODS

3.1 PARTICIPANTS

The participants were taken from a multi-centre study where FM patients were randomized to a 15-week intervention, with either physical resistance exercise or relaxation therapy twice/week, supervised by a physical therapist. The participating centres were located in Gothenburg, Linköping and Stockholm, the study was registered in clinicaltrials.gov, (identification number: NCT01226784). The studies included in this thesis are based on data collected from participants from the Stockholm cohort, and only patients and age matched controls who participated in the exercise intervention. Descriptive data for the participants in these studies are shown in table 3.1.

Table 3.1. Descriptive data for the cohorts. Means and ranges are presented.

	FM n = 29	HC n = 31	Group differences
Age (years)	49.8 (25-64)	46.3 (20-63)	n.s.
FM duration	8.9 (0.5-19)	n.a.	n.a.
Pain VAS (mm)	45.3 (5-92)	0.6 (0-10)	$p<0.0001$
FIQ score	63.1 (42.5–85.0)	6.8 (0–22.8)	$p<0.0001$

3.2 SELF-REPORT QUESTIONNAIRES

Questionnaires data were assessed to evaluate the difference between the groups at baseline as well as to evaluate the impact the exercise intervention had on pain, FM symptoms as well as depression and anxiety. Data from questionnaires reported in the studies included in the current thesis were pain intensity ratings on visual analogue scale (VAS), fibromyalgia impact questionnaire (FIQ) (Bennett, 2005), Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002) and Short form 36 (SF 36) (Contopoulos-Ioannidis et al., 2009). The

participants rated pain intensity on a 100 mm VAS ranging from no pain (0 mm) to worst imaginable pain (100 mm). The FIQ measures the impact that FM has on patients' daily life including physical functioning, ability to work, depression, anxiety, pain, fatigue and well-being. HADS measure depression (HADS D) and anxiety (HADS A). In SF 36 patients report how they experience their own health related quality of life. There are eight sub-scales but the two reported in the current thesis are the compact scores regarding physical- (SF 36 PCS) and mental health related quality of life (SF 36 MCS).

3.3 PRESSURE PAIN ASSESSMENT

Sensitivity to painful stimuli is a common denominator throughout this thesis. Two different kinds of assessments were performed; PPTs were assessed using a pressure algometer and supra-threshold pressure pain sensitivity (P50), was assessed with a pneumatic pressure pain stimulator.

3.3.1 Pressure algometry

In studies II and III PPTs were assessed using pressure algometry (Kosek et al., 1993). The pressure algometer (Somedic sales AB) has a gun shaped handle with a 1 cm^2 circular flat rubber tip on the end. It has a display that informs the experimenter how forcefully they are pressing and the rate of pressure increase. The chosen rate for studies II and III was approximately 50kPa/s. Participants were given a response button, which was attached to the algometer and they were instructed to press the button as soon as they started to experience the pressure as painful. When participants pressed the button the current pressure froze on the screen. The value in kPa that was shown on the screen was noted as the PPT. PPTs were assessed at m. quadriceps femoris.

3.3.2 P50

The P50 measure is a painful pressure stimulus, which is calibrated individually. It was used as measure of pressure pain sensitivity in studies I and IV and implemented in an event-related fMRI paradigm in study IV. In study IV, P50 was used to assess changes in pain

processing following the exercise intervention. The pressure pain stimulation was applied at the thumbnail using an automated, pneumatic, computer controlled stimulator with a plastic piston that applies pressure via 1cm^2 hard rubber probe (Jensen et al. 2009). This apparatus allowed for an individual calibration of a pressure intensity corresponding to the participant's 50 mm rating on a 100 mm VAS scale (Jensen et al., 2009). We chose to use painful pressure stimuli calibrated to correspond to the same rated pain intensity in all individuals since the (BOLD) response has been found to correspond to experienced pain and not the absolute pressure (Gracely et al., 2002). Also on the individual level there are large interindividual differences in pressure pain sensitivity (Kosek et al., 1993) and this measure also surpasses this issue.

3.4 FMRI AND THE BOLD RESPONSE

Magnetic resonance imaging utilises the magnetic properties of protons to create images of the brain. This relies on three magnetic fields, firstly a strong static field, causing magnetically sensitive protons to align. To have all protons behaving alike is important in order to detect disturbances caused by the radiofrequency pulse sequence. The pulse sequence disturbs the alignment of the protons, and a receiver coil detects how long it takes for the hydrogen atoms to go back to their original alignment caused by the static magnetic field. Spatial information cannot be inferred from the MR signal picked up by the receiver coil, in order to do gain this, a gradient field is introduced causing different spatial locations to contribute differently to the MR signal over time. The gradient field is made up of three magnetic gradients at all three spatial dimensions, which alters the strength of the static magnetic field. This provides the ability to detect where the signal is coming from (Huettel et al., 2009). BOLD (the blood oxygen level dependent) fMRI is a way of indirectly measure neuronal activity. It is indirect, as the BOLD response is not a measure neuronal activity per se, but a measure of the haemodynamic response. This is made possible by the fact that the haemodynamic response and neuronal activity is closely linked (Ogawa et al., 1992).

Following neuronal activity, there is an over-compensatory flush of oxygen rich blood that reaches active regions of the brain. There is a difference in magnetic properties between oxygenated blood and deoxygenated blood, i.e. oxygenated blood is diamagnetic and deoxygenated blood is paramagnetic. Paramagnetism will affect the alignment of protons causing the MR signal to be weaker than from areas of the brain that are active and by consequence rich in oxygenated blood (Huettel et al., 2009).

Following image collection, several steps of pre-processing needs to performed before statistical analysis can commence. Firstly motion correction, in order to control for artefacts caused by participants' head movement whilst lying in the scanner. Spatial normalisation controls for the anatomical differences between individual brains, and data from each participant is warped to fit a template brain, for instance the template from the Montral Neurological Institute (MNI). The final process coping with individual differences is spatial smoothing. A Gaussian kernel is applied which replaces the signal in a voxel with the average of that voxels and voxels encompassing the kernel. In addition, smoothing improves the signal to noise ratio, but it return it also reduces spatial specificity (Huettel et al., 2009).

3.4.1 Resting state fMRI

Resting state fMRI utilises the BOLD response to measure spontaneous activity in the brain at rest. The field of fMRI was largely concerned with task evoked activity up until 1995 when a study by Biswal and colleagues reported that the BOLD signal fluctuated between functionally related brain regions, specifically areas involved in a finger-tapping task also displayed coherent spontaneous activity at rest (Biswal et al., 1995). Later it has been found that the DMN, areas of "association cortex" believed to be implicated in introspection and autobiographical memory (Buckner et al., 2008) deactivates during task performance (Raichle et al., 2001), and importantly for resting state, that this network displays correlated spontaneous brain activity (Greicius et al., 2003). During resting state fMRI participants are instructed to lie still, relax and try not to think of anything in particular. Participants are

typically instructed to lie with their eyes open, closed or fixate on a cross-hair, and the methods are largely comparable (Power et al., 2014). In study I in this thesis, the participants were instructed to lie with their eyes closed. Three different approaches of investigating resting state fMRI were taken in study I, independent component analysis (ICA), SCA, as well as fALFF. ICA is an explorative data driven approach to find networks of connectivity. ICA identifies areas of the brain whose activity covaries as measured by BOLD, and is used as a measure of functional connectivity. Whereas ICA is a data driven approach, SCA was applied in order to look at the connectivity of predefined seed regions defined on the basis of previous findings of their involvement in pain processing. In study I of the current thesis seed regions were chosen that are known to be activated during pain provocation in order to investigate differences in connectivity between FM patients and HC. Lastly fALFF is a measure of the extent to which the BOLD signal's time series oscillates with lower frequencies relative the total frequency spectra. This lower frequency spectra has been proposed to be of functional relevance (Zou et al., 2008, Kim et al., 2013).

3.4.2 Event-related fMRI

During the event-related fMRI in studies II, III and IV, participants engaged in a task or experienced a sensory stimulation. During studies II and III, the SCWT was investigated, the paradigm as described above. In order to tap onto and isolate the processing of the conflict that arises when perceiving the incongruent images, it was important to have a baseline that the task of interest can be contrasted with. In studies II and III the chosen baseline were images with colour words written in the congruent colour. When contrasting incongruent and congruent images the cerebral processing concerning task-irrelevant processes should be removed. During the SCWT, such processing can include colour- and semantic processing. Similarly in study IV, both painful and non-painful pressure stimulation was applied, in order to be able to remove cerebral processing concerning the purely tactile aspects of pressure pain stimulation.

3.5 STROOP COLOUR WORD TEST (SCWT)

The SCWT is a cognitive task where participants are presented with colour words written in either congruent (the word red written in red letters) or incongruent colours (the word red written in yellow) (figure 3.1) (Stroop, 1935). The subjects were instructed to respond to the colour of the letters and not the word that they could read. It is a task that assesses executive functioning where a conflict occurs between a previously well-known action schema, which is reading the word without taking the colour of the text into consideration, and the new rule of ignoring what is written and focusing on the colour.

3.5.1 Distraction induced analgesia during SCWT

In studies II and III the SCWT was used to measure DIA. Two versions of the task were used, one with only congruent images and one with only incongruent images. Both versions lasted 10 minutes, each stimulus was presented on the screen for 2 seconds and the inter-stimulus interval (ISI) was three seconds. Before, during and after the SCWT, PPTs, blood pressure and heart rate were measured. PPTs were assessed twice before starting the task, then once at 60, 180, 300, 420 and 540 seconds into the task and 10 minutes following the task. In order to evaluate the relative change in PPTs over time, all measures were normalized to the first PPT taken before starting the task (i.e., by dividing each PPT with the individual's first PPT assessment (Lannersten and Kosek, 2010)). Heart rate and blood pressure was measured before, at 90, 210, 330 and 450 seconds into the task and 10 minutes following the task.

3.5.2 Cerebral activation patterns during SCWT

For studies II and III, incongruent and congruent images were mixed in an event-related fMRI paradigm. The participants were given a response box with buttons in the matching colours to the words that they were presented with. The presentation of congruent and incongruent images was randomized and inter-stimulus asynchrony was jittered between six and eight seconds. The paradigm is illustrated in figure 3.1. The contrast incongruent – congruent was used to analyse cerebral activation during SCWT.

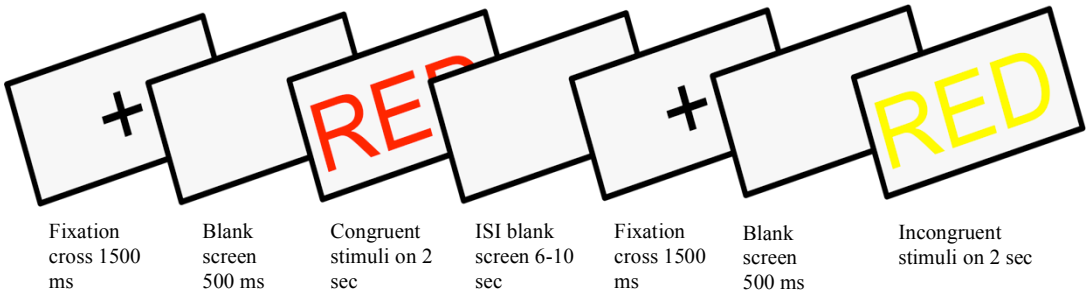

Figure 3.1: Illustration of the event-related SCWT fMRI paradigm.

3.5.3 Cerebral activation patterns during evoked pressure pain (P50)

During fMRI, participants were presented with their individual P50 stimuli as well as a standardized non-painful sensory pressure stimulation corresponding to 50kPa. There were two runs, each lasting 8 minutes and 30 seconds. Participants received pressures corresponding to their P50 pressure and non-painful pressures at 50 kPa. Pressures were delivered in an even-related randomized manner. Stimulus onset synchronicity averaged on 15 seconds and ranged between 10-20 seconds. There were four randomized sequences of jittering, and each participant received two of the four sequences, one in each run, selected at random. The contrast P50 – innocuous pressure stimulation was used to analyse cerebral activation during evoked pain.

3.6 EXERCISE INTERVENTION

A fifteen-week exercise program with two sessions each week was carried out under supervision from physiotherapists (PTs). Before the participants started the intervention, they had an individual meeting with a PT who tested their one repetition maximum (1RM) and tolerance before deciding on the initial load of each exercise. At the same time the participant received individual instructions for each exercise.

Each session lasted for about one hour and included ten minutes of warming up by ergometer cycling, isometric exercises for the deep muscles in back and stomach, and concentric and non-concentric exercises for the legs, back, stomach, arms and hands. The program ended with stretching exercises. The participants' individual 1RM for the different exercises was

tested before starting and at three time points during the program. For the legs and arms the initial load was set at approximately 40 % of one 1RM and the participant was instructed to repeat each exercise 15 to 20 times in two sets within symptom tolerance. Between each set, the participant rested for at least 45 seconds. After five weeks the load was raised up to about 60 % of 1RM with 2 sets of 10-12 repetitions, after eight weeks up to about 70-80% of 1RM with 2 sets of 8-10 or 5-8 repetitions. The body weight was used as load for the back and stomach, which was raised by adding more lever arm. Leg exercises for explosive strength were also included at weeks five and eight.

4 SUMMARY OF STUDIES

4.1 STUDY I

Study I is a resting state study investigating differences in intrinsic brain connectivity between FM (n=16) patients and HC (n=22). Three methods of analysis were employed, seed correction analysis, ICA and fALFF. The seed correlation analysis yielded results both regarding differences between groups as well as regarding individual differences in sensitivity to pain. In the patient group compared to HC, decreased connectivity was found between the thalamus and premotor areas; insula and primary sensorimotor areas, and between supramarginal and prefrontal areas. More specifically, FM patients showed decreased connectivity between the right insula and left primary sensorimotor areas. In both groups, low P50 score (higher pain sensitivity) correlated with connectivity between the insula and DMN as well as the thalamus and DMN.

The initial ICA did not yield any group differences, however a post-hoc analysis, uncorrected for multiple comparisons, found increased connectivity in the FM patients between the EAN and DMN, as well as increased connectivity between the right motor cortex and the postcentral gyrus. fALFF did not reveal any differences between the groups.

The results show that even at rest FM patients show patterns of activation, which are discernable from that of HC. Speculatively, our observation of a reduction

of functional connectivity between sensorimotor areas and anterior insula could be interpreted as if the ‘‘interoceptive thermostat’’ (Craig, 2009) in the anterior insular cortex is impaired in terms of integrating and modulating signals from sensory cortex, which could contribute to altered cerebral processing with relevance for pain perception.

4.2 STUDY II

There were two parts to this study, first to investigate DIA and the second was to investigate performance, as measured by RTs, on the SCWT and how this related to cerebral processing. 29 FM patients and 31 HC were included in the study.

Regarding DIA; FM patients were found to be significantly more sensitive to pressure pain than HC. This was true throughout the paradigm, during both conditions (congruent and incongruent stimuli). PPTs increased over time in both groups, but there were no significant effects of group or condition, nor were there any significant interactions between the factors. The results indicate normal DIA in FM patients.

When compounding cerebral activation contrasting incongruent – congruent stimuli for both groups together, the fMRI results yielded activation patterns in areas of the brain frequently found to be activated during the SCWT, including the dorsal ACC (dACC), insula and DLPFC. No areas of the brain yielded more activity in FM patients, but the healthy controls had more activity in the caudate nucleus and temporal areas encompassing the hippocampus and lingual gyrus. Behaviorally there was no difference between the groups concerning right and wrong answers, however the patient group had significantly RTs for both types of stimuli and the interaction between stimuli and group turned out to be significant, indicating slower speed of processing as well as worsening performance related to more difficult stimuli. The caudate nucleus and hippocampus are areas of the brain involved in learning, which could be related to performance on the SCWT, as performance on this test is reliant of the ability of learning a new action schema.

4.3 STUDY III

As in study II there were two parts to this study, namely investigating the effects of a 15 week exercise intervention on DIA as well as performance and cerebral processing related to the SCWT in FM (n= 19) and HC (n=20). In accordance with our hypothesis, we found evidence that resistance exercise reduced FM symptoms as reflected by lower FIQ values. Regarding

DIA, the results from study II were reproduced also following exercise, but the exercise intervention did not have an impact on DIA in either group.

Both groups improved their performance on the SCWT following exercise, but in different ways. The HC improved speed of processing in both conditions, but the difference in reactivity between the stimuli remained the same. No change in processing speed was found in the FM group. However, there was a difference in reactivity between the first time of measurement and the second, e.g. the gap between RTs for incongruent and congruent images was smaller following the exercise intervention in FM patients than before and there was no longer a statistically significant group difference in reactivity following exercise. The result was interpreted as a specific improvement of cognitive processing related to task difficulty in the FM group. This was accompanied by an increased activity in the left amygdala. The amygdala is an area of the brain that is implicated in arousal, and the behavioural results indicate a better ability to process more difficult stimuli. In combination these results were interpreted as an increased reactivity during a more cognitively challenging task.

4.4 STUDY IV

This study was concerned with cerebral processing of pressure pain both before and following a 15 week exercise intervention in FM (n=18) and HC (n=18). As expected, FM patients had lower P50 scores than HC both before and following the intervention. Following the intervention, P50 scores increased in both groups, but the increase only reached statistical significance in the patient group.

When pooling together pressure pain evoked activity for both groups at baseline, the fMRI results found activity in areas of the brain which are frequently associated with processing pain, including the sensory cortices, insula, ACC and thalamus. When comparing the groups at baseline no areas of the brain were more activated in the FM group, but the HC had higher

activity in the thalamus when contrasting painful with non-painful stimuli. This result differs from Jensen et al's work from 2009 that found a reduced activation of both the thalamus and the rACC. We found no evidence that the exercise intervention had an effect on the cerebral processing of evoked pain in either group. Therefore, our data did not support increased activation in descending pain inhibitory systems, but rather suggest that the exercise intervention influenced peripheral mechanisms.

5 GENERAL DISCUSSION

5.1 STUDIES OF FUNCTIONAL CONNECTIVITY DURING RESTING STATE IN FM

Studies of functional connectivity during resting state can add to our understanding of the integrity of relevant functional networks on the basis of region activity synchronization in healthy subjects and to identify abberations in patient populations. The resting state literature on FM is still scarce, and recent studies report somewhat conflicting results (Napadow et al., 2010, Cifre et al., 2012, Napadow et al., 2012, Pujol et al., 2014). The main finding of study I was that FM was associated with decreased connectivity between pain related and sensorimotor brain areas, more specifically between insula and primary sensorimotor areas (SI/MI). The anterior insula has been implicated in interoception (Craig, 2009) and integration of stimulus-driven and top down driven information (Gu et al., 2013). Speculatively, our findings of reduced functional connectivity between sensorimotor areas and anterior insula could be interpreted as an impairment of the "interoceptive thermostat" in the anterior insula in FM, leading to aberrant integration of modulating signals from sensory cortex. We propose that diminished resting-state connectivity between the insula and the primary somatosensory cortices could reflect a state of mind in which brain areas essential for processing and perception of pain operate under less constraint by other brain networks, particularly those involved in sensory processing. Our suggestion is in accordance with the findings of Pujol et al. who could show a strong association between the intensity of clinical pain and a general weakening of sensory integration during resting state in FM patients (Pujol et al., 2014).

Furthermore, we found that a higher sensitivity to evoked pressure pain correlated with increased connectivity between the insula and midline regions of the DMN as well as the between thalamus and the DMN in FM patients and healthy controls. Increased resting state connectivity between insula and DMN has previously been reported in FM patients compared to healthy controls and was related to higher intensities of spontaneous ongoing pain in FM

patients (Napadow et al., 2010). Following a treatment intervention, a positive correlation was found between the reduction of clinical pain and reduced connectivity between insula and the DMN (Napadow et al., 2012). Taken together, the results from our study and those of Nadapow et al (2010;2012) indicate that the degree of resting state connectivity between insula and the DMN could be of relevance for the experience of ongoing as well as evoked pain in humans. Further support comes from a study from the same group using arterial spin labeling in patients suffering from chronic low back pain (CLBP) and healthy controls (Loggia et al., 2013). The authors reported stronger resting state connectivity between the DMN and right insula in CLBP patients compared to controls. Furthermore, patients with greater connectivity between DMN and insula reported higher ratings of spontaneous clinical pain and following pain provoking manoeuvres patients with a greater increase in back pain also had a greater increase in connectivity between the DMN to the right insula (Loggia et al., 2013).

One aim of our study was to investigate if we could reproduce the findings reported by Nadapow et al. (2010) regarding increased resting state connectivity between insula and the DMN as well as the insula and EAN in FM patients compared to controls. Despite the use of several different methods and low threshold settings this was not the case. Experimental differences between the two studies and differences in the age of the cohorts studied could partly explain the discrepancies. However, the somewhat conflicting results regarding resting state functional connectivity in FM patients call for caution when interpreting the results.

5.2 DISTRACTION INDUCED ANALGESIA (DIA)

Study II is to the author's knowledge the first study to show that DIA is functional in FM. Structures that have been found to be implicated in DIA in healthy controls are the OBFC, ACC, thalamus and PAG (Petrovic et al., 2000, Valet et al., 2004) and in addition DLPFC in FM (Ellingson et al., 2012). As reviewed in the introduction, the ACC, thalamus and PAG have been reported to show attenuated responses in FM patients both when anticipating a

painful stimulation (Loggia et al., 2014) and when experiencing a painful stimulation (Jensen et al., 2009). FM patients had dysfunctional pain inhibitory mechanisms compared to controls during painful stimulation (dysfunctional CPM) (Kosek and Hansson, 1997, Lautenbacher and Rollman, 1997) as well as painful muscle work (dysfunctional EIH) (Kosek et al., 1996a, Staud et al., 2005, Lannersten and Kosek, 2010). Failing to activate CPM and EIH in FM patients could reflect a ceiling effect, i.e., an inability to further activation due to an already ongoing activation of these systems as a result of ongoing chronic pain (Jensen et al., 2009, Lannersten and Kosek, 2010). Another possibility is that pain facilitatory mechanisms are recruited by the painful stimuli overriding the descending inhibition (Lannersten & Kosek 2010). The results from the current studies (II, III), showing that FM patients were able to modulate pain sensitivity during a cognitive task would suggest the latter. Speculatively, higher order cortical areas such as the OBFC or DLPFC are activated normally in FM patients during cognitive tasks such as SCWT, and recruit the ACC and PAG to induce hypoalgesia. The fact that DIA was independent of the cognitive demand/load suggests that distraction of attention away from painful stimuli, rather than engaging in the cognitive task per se was mediating the decreased pain sensitivity.

5.3 SELF-REPORTED MEASURES AND PAIN SENSITIVITY BEFORE AND FOLLOWING THE EXERCISE INTERVENTION

As expected, FM patients had significantly higher ratings of pain intensity, depression, anxiety and lower health related quality of life compared to controls. In accordance with our hypothesis, we found evidence that resistance exercise reduced FM symptoms as reflected by lower FIQ values, but the change in VAS ratings of spontaneous pain intensity related to FM failed to reach statistical significance. The latter is most likely due to the small sample size of this fMRI subgroup, since a significant reduction of pain intensity rated on VAS was seen following resistance exercise when the whole study cohort, including all sites was analysed (Larsson A et al., abstract EULAR 2014). In this cohort, no statistically significant change was found regarding depression/anxiety and only a marginal improvement of the physical

compact of health related quality of life (SF-36 PCS) was seen in FM patients following the exercise intervention. Resistance exercise has previously been found to improve depression and anxiety scores in FM (Gavi et al., 2014), however, since our FM patients had low baseline ratings of depression and anxiety major improvements would not be expected. As expected and in accordance with previous studies (Kosek et al., 1995, Gracely et al., 2002, Jensen et al., 2009), FM patients had increased pressure pain sensitivity compared to controls. However, a statistically significant increase in the absolute pressure needed to elicit moderate pain (50mm on a 100mm VAS = P50) was only seen in the FM group following exercise, indicating that FM patients had a reduction of pressure pain sensitivity following the exercise intervention.

5.4 CEREBRAL ACTIVATION PATTERNS DURING THE SCWT BEFORE AND FOLLOWING EXERCISE INTERVENTION

FM patients had longer RTs for both the congruent and incongruent condition compared to controls, as expected, and the interaction, i.e., patients performing even worse for incongruent trials implies a dysfunction in processing distractions, which is in line with previous suggestions and findings (Leavitt et al., 2002, Leavitt and Katz, 2006). Contrary to the two earlier studies on cognition in FM (Glass et al., 2011, Seo et al., 2012), no group differences were found in the ACC or frontal regions, instead decreased activation in the caudate and hippocampus was found in FM patients compared to controls when contrasting incongruent and congruent stimuli. Dopamine deficiency of the caudate has previously been suggested to be an underlying mechanisms of the cognitive dysfunctions of Parkinson's disease (Grahn et al., 2008). Furthermore reduced concentrations of dopamine metabolite have been found in FM (Legangneux et al., 2001), and a dopamine agonist has showed promising results in FM (Holman and Myers, 2005), which suggests dopamine deficiency as a possible explanation for our findings. An elegant study published by Rieckmann and colleagues in 2011 investigated D1 receptor density in the caudate, a seed based connectivity analysis from the DLPFC and performance on a WM task in both younger and older adults. They could report

that older adults performed worse than the younger adults on the WM task, and this related to both lower D1 receptor density in the caudate as well as decreased connectivity between the DLPFC and parietal cortex (Rieckmann et al., 2011). There are several known cortico–striato-thalamo-cortical loops, one of which links the associative areas of the PFC via the caudate to sensorimotor areas (Joel and Weiner, 2000). To our knowledge, this has not been specifically assessed in FM patients, but deficiencies in the fronto-parietal network during a cognitive task have been reported in FM patients (Glass et al., 2011, Seo et al., 2012) as well as task related activation of the caudate in HC, but not FM (Seo et al., 2012).

This suggests that the mechanisms behind poorer cognitive performance in FM can be similar to that of older adults (Rieckmann et al., 2011). Intriguingly, the fronto-parietal network has also been found to be implicated in pain modulation (Wager et al., 2011, Kong et al., 2013) and decreased activity in the caudate as well as the fronto-parietal network as reviewed above, provides a hypothetical link between the pain- and cognitive difficulties in FM syndrome.

In accordance with our hypothesis, the performance on the SCWT had improved for both groups following the 15-week exercise intervention. However the groups differed in that the HC improved in RTs for both stimuli, indicating improved processing speed, whereas the FM patients had a specific improvement of their reactivity to the incongruent stimuli. Considering earlier reports of FM patients having especial perturbation to their ability for executive functioning (Glass, 2009), and that exercise has a particular positive effect on this aspect of cognition (Hillman et al., 2008), our results support the reasoning that FM patients should have a particular benefit of physical exercise on their cognitive capacity.

Contrary to our hypothesis, the improvement in RTs related to task difficulty was not accompanied by increased activation of caudate nucleus or hippocampus, instead FM patients had an increased task related activation of left amygdala, i.e., the amygdala showed greater

reactivity to incongruent stimuli than congruent stimuli following exercise in FM patients, but not in healthy controls.

The amygdala is closely linked to the function of the autonomic nervous system (ANS) (Beissner et al., 2013) as well as the HPA-axes (Flandreau et al., 2012). Dysregulation of the ANS and the HPA-axes has been reported in FM patients (Kadetoff and Kosek, 2010). More specifically, FM patients have an autonomic imbalance characterized by a relative basal sympathetic hyperactivity and parasympathetic hypoactivity, combined with sympathetic hyporeactivity during stress or physical exercise (Riva et al., 2010). Longitudinal studies have shown that long-term physical exercise increases parasympathetic activity in healthy women (Earnest et al., 2008) and have beneficial effects on the HPA-axis (Puterman et al., 2011). The same has been shown in FM patients following 16 weeks of resistance exercise training (Figueroa et al., 2008), thus normalizing the basal sympathetic hyperactivity in the patient group. Left amygdala has been implicated in the regulation of autonomic activity, particularly the sympathetic tone (Thayer et al., 2012, Beissner et al., 2013). Therefore, normalization of the autonomic activity following exercise would hypothetically be accompanied by a reduction (normalization) of basal activity in amygdala potentially increasing the reactivity of amygdala. Amygdala is involved in arousal (Zald, 2003) and cognitive functioning (LeDoux, 2007) so the increased task related activation of the amygdala could hypothetically have conferred the better performance of FM patients to the more demanding stimuli. We hypothesize that if the basal activation level of amygdala was reduced following the exercise intervention in FM patients, allowing for greater reactivity, the increased activation of amygdala during the incongruent tests in FM patients could be regarded as a compensatory mechanism and thus be related to the better performance on the more demanding task.

5.5 PAIN PROCESSING BEFORE AND FOLLOWING EXERCISE

The last study in this thesis is part of a greater effort aiming at assessing the mechanisms of action of the most common treatments of FM, such as pharmacological treatments, CBT and

in this study exercise using an evoked pain fMRI paradigm (Jensen et al., 2012b, Jensen et al., 2014). One aim of this study was to see if we could replicate our previous findings regarding altered cerebral processing of pressure pain in FM patients (Jensen et al. 2009). In accordance with our previous study, we found reduced pain related activation of thalamus in FM patients, but we could not replicate our finding of the reduced rACC activation, despite very liberal thresholds. The most likely explanation is recruitment bias since patients with severe FM are more unlikely to volunteer for a 15-week exercise intervention study. In accordance with our hypothesis, we found an improvement of FM symptoms following the exercise intervention and this was accompanied by reduced pressure pain sensitivity in the FM group. Despite the fact that FM patients received significantly higher absolute pressure stimuli during fMRI following compared to before the exercise intervention, no differences in pain related brain activations were seen. The finding that resistance exercise reduced pressure pain sensitivity and FM severity without affecting pain related cerebral activation patterns would support the conclusion that the improvement following the exercise intervention was mainly mediated by peripheral mechanisms. The latter is supported by muscle microdialysis data from this multicenter, randomized study showing reductions in muscle metabolites and algogenic substances following the exercise intervention in FM patients (Gerdle et al, 2015 submitted).

5.6 SUMMARY AND CONCLUSIONS

Studies I, II and IV all report data collected from patients within the same cohort and they all show attenuated cortical activation in FM patients, at rest, during the SCWT and during pain provocation, adding to a substantial line of evidence reviewed in the introduction, that CNS disturbances are highly implicated in FM syndrome. The results from the exercise intervention provide further knowledge regarding the importance of physical exercise in FM. It improved both SCWT performance as well as decreasing pressure pain sensitivity. Captivatingly though no areas of the brain showed an increase in activation following the

improvement regarding pressure pain, but for SCWT performance the amygdala showed higher activity. The amygdala results might indicate an improvement of ANS reactivity, but the HRV data are in the process of being analyses and therefore at this time no data can support or contradict this notion. The ANS might also be implicated in the decreased hyperalgesia, as increased reactivity might influence the peripheral mechanisms that have been suggested to contribute to pain following muscle work in FM such as decreased blood flow (Elvin et al., 2006).

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